

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k111976

B. Purpose for Submission:

To obtain a substantial equivalence determination for this premarket notification for the addition of Erythromycin to the VITEK 2 and VITEK 2 Compact Antimicrobial Susceptibility Test (AST) Systems.

C. Measurand:

Erythromycin concentrations of 1, 2, 4 and 16 µg/mL are included in the VITEK[®] 2 VITEK 2 Streptococcus Erythromycin card.

D. Type of Test:

The minimum inhibitory concentration (MIC) determined using qualitative growth based detection algorithm with predetermined growth threshold. The MIC reporting result range of the card is ≤ 0.12– ≥8 µg/mL.

E. Applicant:

bioMerieux, Inc.

F. Proprietary and Established Names:

VITEK[®] 2 Streptococcus Erythromycin

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
LON	Class II	21 CFR 866.1645	Microbiology

H. Intended Use:

1. Intended use(s):

VITEK[®] 2 Streptococcus Erythromycin is designed for antimicrobial susceptibility testing of *Streptococcus* species. VITEK[®] 2 Streptococcus

Erythromycin is a quantitative test intended for use with the VITEK[®] 2 and VITEK[®] 2 Compact Systems as a laboratory aid in the determination of *in vitro* susceptibility to antimicrobial agents. Erythromycin has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for this antimicrobial.

Active *in vitro* and in clinical infection:

Streptococcus pneumoniae
Streptococcus pyogenes

Active *in vitro* but clinical significance is unknown:

Viridans group Streptococci

2. Indication(s) for use:

VITEK[®] 2 Streptococcus Erythromycin is designed for antimicrobial susceptibility testing of *Streptococcus* species. VITEK[®] 2 Streptococcus Erythromycin is a quantitative test intended for use with the VITEK[®] 2 and VITEK[®] 2 Compact Systems as a laboratory aid in the determination of *in vitro* susceptibility to antimicrobial agents. Erythromycin has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for this antimicrobial.

Active *in vitro* and in clinical infections:

Streptococcus pneumoniae
Streptococcus pyogenes

Active *in vitro* but clinical significance is unknown:

Viridans group Streptococci

The VITEK[®] 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK[®] 2 Systems for the automated quantitative or qualitative susceptibility testing of isolated colonies for the most clinically significant aerobic gram-negative bacilli, *Staphylococcus* spp., *Enterococcus* spp., *Streptococcus* spp. and clinically significant yeast.

3. Special conditions for use statement(s):

For prescription use only.

4. Special instrument requirements:

For use with the VITEK[®] 2 and VITEK[®] 2 Compact Systems

I. Device Description:

The VITEK 2 AST card is a miniaturized, abbreviated and automated version of the doubling dilution technique for determining the minimum inhibitory concentration (MIC). Each VITEK 2 AST card contains 64 wells. A control well which contains only microbiological culture media is resident on all cards. The remaining wells contain premeasured portions of a specific antibiotic combined with culture media. The bacterial or yeast isolate to be tested is diluted to a standardized concentration with 0.45 – 0.5% saline before being used to rehydrate the antimicrobial medium within the card. The VITEK 2 System automatically fills, seals, and places the card into the incubator/reader. The VITEK 2 Compact has a manual filling, sealing and loading operation. The VITEK 2 Systems monitor the growth of each well in the card over a defined period of time. At the completion of the incubation cycle, a report is generated that contains the MIC value along with the interpretive category result for each antibiotic contained on the card.

The VITEK 2 Streptococcus Erythromycin has the following concentrations in the card: 1, 2, 4, and 16 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK 2 card is $\leq 0.12 - \geq 8$ µg/mL.

The MIC ranges, interpretive criteria and equivalent concentrations are as follows for *Streptococcus pneumoniae* and *Streptococcus* species:

VITEK 2 AST-ST	Equivalent Standard Method Concentration by Efficacy in µg/mL	MIC Ranges and FDA/CLSI Categories MIC* in µg/mL:		
		S*	I	R
Erythromycin	1, 2, 4, 16	≤ 0.25	0.5	≥ 1

* S = Susceptible; I = Intermediate; R = Resistant

J. Substantial Equivalence Information:

1. Predicate device name(s):

VITEK 2 AST-GP Amoxicillin for *S. pneumoniae*

2. Predicate K number(s):

k063597

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Determining quantitative and qualitative susceptibility to antimicrobial agents	Same
Inoculation and test organism	Isolated colonies of <i>Streptococcus</i> species	Same
Instrument	Test are run on both the VITEK 2 and VITEK 2 Compact Systems	Same
Test Card	The VITEK 2 card, including base broth	Same
Test Method	Automated quantitative Antimicrobial susceptibility test to determine the <i>in vitro</i> susceptibility of <i>Streptococcus</i> species.	Same

Differences		
Item	Device	Predicate
Antibiotic	Erythromycin-specific concentrations	Amoxicillin-specific concentrations
Reading algorithm	Unique to Erythromycin	Unique to Amoxicillin

K. Standard/Guidance Document Referenced:

“Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA”

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071462.pdf>

Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard -8th Edition, Document M7-A8.

Performance Standards for Antimicrobial Susceptibility Testing – 19th Informational Supplement, M100-S21.

L. Test Principle:

Automated growth based detection using attenuation of light measured by an optical scanner. The optics used in the systems use visible light to directly measure organism growth. Transmittance optics are based on an initial light reading of a well before significant growth has begun. Periodic light transmittance samplings of the same well measure organism growth by how much light is prevented from going through the well. The VITEK 2 System monitors the growth of each well in the card over a defined period of time. An interpretive call is made between 4 and 16 hours for a “rapid” read but may be extended to 18 hours in some instances. At the completion of the incubation cycle, a report is generated that contains the MIC value along with the interpretive category result for each antibiotic on the card. The VITEK 2 Streptococcus Erythromycin has the following concentrations in the card: 1, 2, 4, and 16 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK 2 card is $\leq 0.12 - \geq 8$ µg/mL.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

A reproducibility study was conducted at three external clinical sites. Ten *Streptococcus* species isolates were tested at each site and testing was performed in triplicate over three days with the VITEK 2 Streptococcus Erythromycin card. The testing was performed using both the manual dilution method and the automated dilution mode. Testing was conducted on the VITEK 2 instrument.

For the sake of reproducibility calculations, off-scale values are handled in two ways; “best case” and “worst case” scenarios. Best case calculation for reproducibility assumes the off-scale result is within one well from the mode MIC value. Worst case calculation for reproducibility assuming the off-scale result is greater than one well from the mode MIC value.

The overall reproducibility was >95% with +/- one dilution observation for the VITEK 2 and the VITEK 2 Compact system. Only Manual Dilution testing was conducted since the VITEK 2 Compact system does not have a functionality to support automatic dilution to inoculate the card. Results were as follows:

VITEK System	Inoculation Method	Best Case	Worst Case
VITEK 2	Auto-Dilution	96.7%	96.7%
	Manual	96.3%	96.3%
VITEK 2 Compact	Manual	97.4%	97.4%

b. *Linearity/assay reportable range:*

Not applicable

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

The recommended *Streptococcus pneumonia* QC organism was tested on every test occasion with the reference method and the VITEK 2 System. Ancillary quality control testing was also performed. Two gram-positive organisms were tested throughout comparative testing at each study site by the reference method only. This was done to perform further quality control of the broth microdilution panels using *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213 which have a QC range of 1-4 µg/mL and 0.25-1 µg/mL, respectively.

The reference method QC results were in range for every day tested. The VITEK 2 was tested a sufficient number of times to demonstrate that the system can produce QC results in the recommended range.

Quality Control was performed during the studies using both the auto-dilution and the manual method of diluting the organisms on the VITEK 2 System. Results demonstrated that methods were comparable.

Quality Control Results with the VITEK 2 System for Erythromycin were as follows:

Organism	Concentration (µg/mL)	Auto Dilution		Manual Dilution	
		Reference	VITEK 2	Reference	VITEK 2
<i>Streptococcus pneumonia</i> ATCC 49619 Acceptable MIC range: 0.03-0.125 µg/mL	≤0.03	45		46	
	0.06	168		168	
	0.125	1		1	
	≤0.125*		214		215
	0.25*				
	0.5*				
	1,2,4,8				

* VITEK Card Result Range is ≤ 0.125 – ≥ 8

The Quality control organism was in control in the reference on all days. Quality Control results for the VITEK 2 System using either inoculation dilution were at $\leq 0.125 \mu\text{g/mL}$ 100% of the time.

A similar QC study was conducted to evaluate the VITEK 2 Compact System. Results were compared to the expected FDA/CLSI QC results. All results for the VITEK 2 Compact System were within the expected QC ranges 100% of the time.

Inoculum density control was monitored using the DensiChek2 instrument. This was standardized weekly with all results recorded and in the expected range.

d. Detection limit:

Not applicable.

e. Analytical specificity:

Not applicable.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Performance was established through a clinical study which was conducted at four external study sites. A total of 1103 clinical isolates were tested by VITEK® 2 Streptococcus Erythromycin with the VITEK® 2 System. The majority of the isolates were recently isolated from clinical specimens. One hundred and ninety six of the 1103 clinical isolates tested were stock isolates (17.8%). A challenge set consisting of 112 isolates was evaluated with VITEK® 2 Streptococcus Erythromycin. Testing of clinical isolates was performed using the automated method of inoculation and the challenge organisms were tested with both the manual dilution and automatic dilution. Each isolate was tested by the VITEK 2 Streptococcus Erythromycin and the CLSI broth microdilution reference method. The inoculum was prepared with direct colony suspension. A comparison was provided to the reference method with the following agreement. Three very major errors and three major errors were seen. The error rates are acceptable based on the recommended performance in the AST Guidance Document. No growth was observed in 9 isolates.

Auto Dilution

Organism Group	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	# vmj	# maj	# min
<i>Streptococcus</i> species												
CLINICAL	1103	1079	98.7	114	101	88.6	1087	98.5	309	3	3	11
CHALLENGE	112	111	99.1	6	6	100	112	100	42	0	0	0
COMBINED (CLINICAL AND CHALLENGE)	1215	1190	97.9	120	107	89.2	1199	98.7	351	3	3	11

EA-Essential Agreement **CA**-Category Agreement maj-major discrepancies

Vmj-very major discrepancies **min**-minor discrepancies

A high agreement was observed for both clinical and challenge isolates with a total EA of 97.9%, and evaluable EA of 89.2% and a CA of 98.7%. This level of evaluable EA is acceptable since CA was very high.

Performance of the VITEK® 2 and the VITEK® 2 Compact was also evaluated with the same 112 challenge organisms using the manual dilution method. A comparison was provided to the reference method with the following agreement as shown below

Manual Dilution (VITEK 2)

Organism Group	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	# vmj	# maj	# min
<i>Streptococcus</i> species												
CHALLENGE	112	112	100	5	5	100	110	98.2	35	0	0	2

Manual Dilution (VITEK 2 Compact)

Organism Group	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	# vmj	# maj	# min
<i>Streptococcus</i> species												
CHALLENGE	112	111	99.1	5	5	100	112	100	42	0	0	0

b. Matrix comparison:

Not Applicable

3. Clinical Studies:

a. *Clinical Sensitivity:*

Not Applicable

b. *Clinical specificity:*

Not Applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Not Applicable

4. Clinical cut-off:

Not Applicable

5. Expected values/Reference range:

According to CLSI and the most updated Erythromycin drug label, the breakpoints for *Streptococcus* species, including *S. pneumoniae* are:

≤ 0.25 (S), 0.5 (I), ≥ 1 (R)

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR section 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.